

# Skin prick test responses and allergen-specific IgE levels as predictors of peanut, egg, and sesame allergy in infants

Rachel L. Peters, MPH,<sup>a,b</sup> Katrina J. Allen, BMedSc, MBBS, FRACP, FAAAAI, PhD,<sup>a,b,c</sup>  
 Shyamali C. Dharmage, MBBS, MSc, MD, PhD,<sup>a,d</sup> Mimi L. K. Tang, MBBS, FRACP, FRCPA, PhD,<sup>a,b,c</sup>  
 Jennifer J. Koplin, PhD,<sup>a,b</sup> Anne-Louise Ponsonby, BMedSci, MBBS, PhD,<sup>a,b,d</sup> Adrian J. Lowe, PhD,<sup>a,d</sup>  
 David Hill, MBBS, FRACP,<sup>a</sup> and Lyle C. Gurrin, PhD,<sup>a,d</sup> for the HealthNuts study Melbourne, Australia

**Background:** Ninety-five percent positive predictive values (PPVs) provide an invaluable tool for clinicians to avoid unnecessary oral food challenges. However, 95% PPVs specific to infants, the age group most likely to present for diagnosis of food allergy, are limited.

**Objective:** We sought to develop skin prick test (SPT) and allergen-specific IgE (sIgE) thresholds with 95% PPVs for challenge-confirmed food allergy in a large population-based cohort of 1-year-old infants with challenges undertaken irrespective of SPT wheal size or previous history of ingestion.

**Methods:** HealthNuts is a population-based, longitudinal food allergy study with baseline recruitment of 1-year-old infants. Infants were recruited from council-run immunization sessions during which they underwent SPTs to 4 allergens: egg, peanut, sesame, and cow's milk/shrimp. Any infant with a detectable SPT response was invited to undergo oral food challenge and sIgE testing.

**Results:** Five thousand two hundred seventy-six infants participated in the study. Peanut SPT responses of 8 mm or greater (95% CI, 7-9 mm), egg SPT responses of 4 mm or greater (95% CI, 3-5 mm), and sesame SPT responses of 8 mm or greater (95% CI, 5-9 mm) had 95% PPVs for challenge-proved food allergy. Peanut sIgE levels of 34 kU<sub>A</sub>/L or greater

(95% CI, 14-48 kU<sub>A</sub>/L) and egg sIgE levels of 1.7 kU<sub>A</sub>/L or greater (95% CI, 1-3 kU<sub>A</sub>/L) had 95% PPVs for challenge-proved food allergy. Results were robust when stratified on established risk factors for food allergy. Egg SPT responses and sIgE levels were poor predictors of allergy to egg in baked goods.

**Conclusion:** These 95% PPVs, which were generated from a unique dataset, are valuable for the diagnosis of food allergy in young infants and were robust when stratified across a number of different risk factors. (J Allergy Clin Immunol 2013;■■■:■■■-■■■.)

**Key words:** Food allergy, skin prick test, serum-specific IgE, oral food challenge, predictive value of tests, egg, baked egg, peanut, sesame

IgE antibody levels, as determined based on either skin prick test (SPT) responses or serum allergen-specific IgE (sIgE) levels, are poorly correlated with the gold standard test for food allergy: the oral food challenge (OFC). Therefore 95% positive predictive values (PPVs) have been developed as a surrogate for the OFC and to minimize both overdiagnosis of food allergy by relying on SPT responses or sIgE levels alone and unnecessary, labor-intensive, and potentially dangerous OFCs.<sup>1,2</sup>

SPT and sIgE 95% PPV thresholds have been reported to be dependent on age, with infants more likely to have lower 95% PPVs than children older than 2 years.<sup>3,4</sup> However IgE-mediated food allergy is most likely to present for diagnosis in the first 2 years of life.<sup>5</sup> To date, there has been a paucity of data on 95% PPVs in this age group. Recently, it has been found that PPVs derived from clinic populations cannot be meaningfully applied to general populations, highlighting the need for population-based PPVs.<sup>6</sup>

The association between SPT responses or sIgE levels and the risk of challenge-confirmed food allergy has not previously been examined in a population sample of 1-year-old infants. Nor have challenges been undertaken systematically in infants with detectable SPT responses, irrespective of the magnitude of wheal size or previous history of ingestion with predetermined, objective stopping criteria.

We aimed to examine the diagnostic value of SPT responses and sIgE levels to challenge-confirmed food allergy in 1-year-old infants recruited from a population-based sample and to develop thresholds above which an infant is highly likely to have food allergy. In addition, we aimed to establish whether these thresholds with 95% PPVs for food allergy were different when stratified by known risk factors for food allergy, including infantile eczema, previous reaction history, sex, vitamin D levels, and family history of allergic disease.

From <sup>a</sup>the Murdoch Childrens Research Institute; <sup>b</sup>the Department of Paediatrics, University of Melbourne; <sup>c</sup>the Department of Allergy and Immunology, Royal Children's Hospital; and <sup>d</sup>the Centre for Molecular, Environmental, Genetic and Analytic Epidemiology, University of Melbourne.

Supported by funding from the National Health and Medical Research Council (NHMRC) of Australia, the Ilhan Food Allergy Foundation, AnaphylaxisStop, the Charles and Sylvia Viertel Medical Research Foundation, and the Victorian Government's Operational Infrastructure Support Program. K.J.A. is a Viertel senior medical research fellow. R.L.P. is an Australian Postgraduate Award scholar. L.C.G., J.J.K., A.J.L., A.-L.P., and S.C.D. hold NHMRC awards.

Disclosure of potential conflict of interest: K. J. Allen is a board member for Ilhan Food Allergy Foundation and has received payment for lectures, including service on speakers, bureaus for Pfizer, Nutricia, Annual Women's Update, and Abbott. M. L. K. Tang has received grants from the National Health and Medical Research Council (NHMRC) and is an allergist, immunologist, and immunopathologist who performs skin prick testing and serum allergen-specific IgE testing in work. A.-L. Ponsonby has received grants from, has grants/grants pending with, and is employed by the NHMRC. A. J. Lowe has received grants from NHMRC for project grant funding. The rest of the authors declare that they have no relevant conflicts of interest.

Received for publication December 18, 2012; revised May 21, 2013; accepted for publication May 31, 2013.

Corresponding author: Katrina J. Allen, BMedSc, MBBS, FRACP, FAAAAI, PhD, Murdoch Childrens Research Institute, Royal Children's Hospital, Flemington Rd, Parkville 3052, Victoria, Australia. E-mail: [katie.allen@rch.org.au](mailto:katie.allen@rch.org.au).

0091-6749/\$36.00

© 2013 American Academy of Allergy, Asthma & Immunology  
<http://dx.doi.org/10.1016/j.jaci.2013.05.038>

**Abbreviations used**

AUC: Area under the curve  
 LR: Likelihood ratio  
 NPV: Negative predictive value  
 OFC: Oral food challenge  
 PPV: Positive predictive value  
 ROC: Receiver operating characteristic  
 sIgE: Allergen-specific IgE  
 SPT: Skin prick test

**METHODS****Study design**

The HealthNuts study is a population-based, longitudinal food allergy study in Melbourne, Australia. The study methods have been described in detail previously.<sup>7</sup> In brief, 5276 infants aged 11 to 15 months were recruited through 131 council-run immunization sessions from September 2007 to August 2011. Infants underwent SPTs to 4 common food allergens, and infants with detectable SPT responses were invited to Melbourne's Royal Children's Hospital for a formal OFC to test for food allergy. Infants with a negative SPT response in the presence of a positive histamine control were considered highly unlikely to have IgE-mediated allergy to these foods and did not undergo OFCs. To validate this assumption, we undertook OFCs in 200 randomly selected SPT negative controls. None had a positive OFC result in the context of negative SPT responses and were subsequently excluded from this analysis. Nurses were blinded to wheal size and previous history of ingestion.

**SPT**

SPTs were administered with a single-tine lancet (Stallergenes, Antony, France) on the infant's back. Tests were performed to 4 foods, peanut, hen's egg, sesame, and either cow's milk or shrimp (ALK-Abelló, Madrid, Spain), along with a positive control (10 mg/mL histamine) and a negative control (saline). Wheal size was measured after 15 minutes and calculated as the average of the longest diameter and the diameter perpendicular to it after subtracting the negative control.

**Serum-specific IgE testing**

Blood samples were collected and plasma was isolated for sIgE assays on the same day. Serum specific IgE antibodies to whole peanut, egg white, and sesame were analyzed by using the ImmunoCAP System FEIA (Phadia AB, Uppsala, Sweden).

**OFCs**

Eighty-three percent of infants with detectable SPT responses at community recruitment accepted the invitation to undergo an OFC. SPTs were repeated on the day of the OFC and used for this analysis; OFCs were conducted as previously described.<sup>7</sup> OFC results were deemed positive if they met the predefined criteria (see definitions) within 2 hours of the last challenge dose. To capture late reactions, parents were instructed to administer a single serving of the challenge food for 7 days and observe for a reaction. The food challenge result was deemed negative if the infant tolerated the top dose of the challenge and did not report a late reaction after consumption of the top challenge dose at home for 1 week or if the infant's parent reported that the infant was regularly consuming and tolerating the food after a negative OFC result. Food challenges were deemed inconclusive and the parents were offered a repeat challenge if the infant refused to ingest the challenge food at the clinic or if the parent reported a late reaction that did not meet the positive challenge criteria yet led the parent to remove the food from the infant's diet. In addition, positive OFC results in infants without any evidence of IgE sensitization to the allergen were also considered inconclusive.

A subset of infants with positive test results to raw egg white were also offered a baked egg challenge ( $n = 185$ ). Recruitment for baked egg challenges began partway through the study, and all infants who had challenge-confirmed allergy to raw egg white were offered an OFC to baked egg in the form of a muffin. Data from baked egg challenges are therefore derived from a consecutive series of infants who had challenge-confirmed raw egg allergy.

**Ethics**

Ethics approval was obtained for the HealthNuts study from the Victorian State Government Office for Children (reference no. CDF/07/492), the Victorian State Government Department of Human Services (reference no. 10/07), and the Royal Children's Hospital Human Research Ethics Committee (reference no. 27047).

**Statistical methods**

The diagnostic capacity of tests for food allergy was assessed by using receiver operating characteristic (ROC) curves; the area under the curve (AUC) was calculated to quantify the accuracy of the test. Logistic regression was used to model the association between the risk of food allergy and the measure of sensitization (either SPT wheal size or sIgE threshold) by assuming a linear relationship between the log of the proportion of patients with food allergy and the numeric measure of sensitization. A fitted probability of food allergy was produced for each participant given their SPT wheal size or sIgE threshold, and these were used to replace the observed binary outcome in the standard formula for the PPV; that is, a modeled PPV for each level of SPT wheal size or sIgE threshold was produced by taking the average of the fitted probability of food allergy for all infants with an SPT wheal size or sIgE threshold of greater than the given level. This method produces a smooth nondecreasing curve for the PPV across the range of SPT wheal sizes and sIgE thresholds. Therefore it overcomes fluctuations (sampling variation) in the observed proportions of infants with food allergy for increasing SPT responses and sIgE levels. To quantify the precision of estimation of the PPVs, we used bootstrapping, a method of deriving SEs and CIs from repeated samples drawn with replacement from the original dataset. Twenty bootstrap replications were used to determine the variability of parameter estimates and to calculate 95% CIs for the thresholds with 95% PPVs to food allergy.

Sensitivity, specificity, negative predictive value (NPV), and positive and negative likelihood ratios (LRs) were calculated for the thresholds that had 95% PPVs to food allergy. Note that these estimates of sensitivity and specificity pertain to the subpopulation who are SPT sensitized and not the general population of all infants. These estimates are still population based because the sample includes all SPT-sensitized infants and not just those with additional symptoms or a history or clinical indication of increased allergic risk, as would be typical of an allergy clinic at a tertiary referral hospital. Data from inconclusive challenges were excluded from the analysis.

The analysis was stratified on known risk factors for food allergy: sex, eczema, vitamin D insufficiency, previous reaction history, and family history of allergic disease or food allergy. Stratum-specific 95% PPV thresholds were compared with the  $z$  test. STATA release 12.0 (StataCorp, College Station, Tex) was used for all analyses.

**Definitions**

*Sensitization* was defined as an SPT response of 2 mm or greater or an sIgE levels of 0.35 kU<sub>A</sub>/L or greater.

A *positive OFC result* was defined as at least 1 of the following: 3 concurrent non-contact urticaria reactions lasting at least 5 minutes, severe persistent vomiting, perioral or periorbital angioedema, or anaphylaxis (evidence of circulatory or respiratory involvement) within 2 hours of the last challenge dose in the presence of a positive test result for sensitization.

*Eczema* was defined as a parent-reported doctor's diagnosis of eczema.

A *previous reaction* was defined as a parent-reported reaction consistent with IgE-mediated food allergy (eg, hives, angioedema, vomiting, and wheezing) within 4 hours of consuming the food.

**TABLE I.** Demographic characteristics of infants who participated in OFCs\*

	Peanut tolerance (n = 290)	Peanut allergy (n = 148)	Egg tolerance (n = 207)	Egg allergy (n = 445)	Sesame tolerance (n = 72)	Sesame allergy (n = 31)
Age at recruitment (mo), mean (SD)	12.6 (0.65)	12.8 (0.88)	12.6 (0.72)	12.6 (0.69)	12.5 (0.47)	12.9 (0.92)
Sex (male)	158/289 (55%)	98/148 (66%)	101/206 (49%)	250/444 (56%)	46/72 (64%)	26/31 (84%)
Eczema diagnosis†	132/261 (51%)	99/138 (72%)	66/176 (38%)	250/408 (61%)	42/67 (63%)	28/31 (90%)
Previous reaction to food‡	8/276 (3%)	20/139 (14%)	24/196 (12%)	116/424 (27%)	0	2/31 (6%)
Infant previously consumed food	83/257 (32%)	30/126 (24%)	186/195 (95%)	375/421 (89%)	33/66 (50%)	13/31 (42%)
Family history of allergic disease§	214/290 (74%)	111/148 (75%)	150/207 (72%)	344/445 (78%)	51/71 (71%)	22/31 (71%)
Family history of food allergy	36/288 (13%)	16/146 (11%)	24/202 (12%)	61/437 (14%)	6/72 (8%)	5/31 (16%)
SPT   (mm)	2 (0-3)	8 (6-10)	0 (0-2)	3.5 (2.5-5)	1 (0-2.5)	7 (4-10)
sIgE   (kU <sub>A</sub> /L)	0.37 (0.06-1.6)	3.89 (1.1-12.4)	0.19 (0.09-0.49)	1.53 (0.51-4.91)	0.93 (0.27-2.85)	6.75 (1.63-14.3)

\*The denominators are not always the same because questionnaire data on demographic factors were missing for some infants.

†Parent-reported doctor's diagnosis of eczema.

‡Previous reaction consistent with IgE-mediated food allergy.

§Immediate family history of asthma, eczema, allergic rhinitis, or food allergy.

||Median SPT response/sIgE level to target food (interquartile range).

**TABLE II.** Diagnostic capacity of SPTs to challenge-confirmed food allergy

Allergen	No.	95% PPV (mm [95% CI])	NPV (% [95% CI])	Sensitivity (% [95% CI])	Specificity (% [95% CI])	Positive LR (95% CI)	Negative LR (95% CI)	AUC (95% CI)
Peanut	435	8 (7.2-9.3)	80 (76-84)	54 (46-62)	98 (95-99)	22.2 (10.5-46.8)	0.47 (0.40-0.56)	0.93 (0.90-0.96)
Egg	650	4 (3.3-5.0)	44 (40-49)	46 (41-50)	93 (89-96)	6.7 (4.0-11.3)	0.58 (0.53-0.64)	0.87 (0.84-0.90)
Baked egg	167	11 (82% PPV)*	82 (75-87)	0 (0-12)	99 (96-100)	-	1.01 (0.93-1.02)	0.65 (0.54-0.77)
Sesame	103	8 (4.6-9.4)	82 (72-89)	48 (30-67)	99 (93-100)	34.8 (4.8-252)	0.52 (0.37-0.74)	0.92 (0.86-0.98)

\*Ninety-five percent PPVs could not be calculated.

*No previous reaction* was defined as occurring in an infant who had not consumed food or had consumed food without a reaction.

*A family history of allergic disease* was defined as occurring in an infant who had an immediate family with a history of either eczema, asthma, allergic rhinitis, or food allergy.

## RESULTS

Of the 7134 infants approached at immunization sessions, the parents of 5276 (74%) agreed to participate. One thousand eighty-nine infants at community recruitment were eligible for assessment at the hospital clinic, and 908 (83%) attended. The prevalence of challenge-confirmed food allergy at the population level was 3.1% (95% CI, 2.6% to 3.6%) to peanut, 10.1% (95% CI, 9.2% to 11.0%) to egg, and 0.7% (95% CI, 0.5% to 0.9%) to sesame.

There was no significant difference in SPT response or reaction history between infants who participated in OFCs and those who declined OFCs (data not shown). There were 457, 694, and 113 peanut, sesame, and raw egg OFCs, respectively (excluding the negative controls). OFCs were deemed inconclusive if parents reported a possible late reaction that did not meet the positive challenge criteria but caused the parents to remove the food from the infant's diet (peanut, n = 5; egg, n = 12; and sesame, n = 4), if the infant refused to eat the challenge food (peanut, n = 11; egg, n = 4; and sesame, n = 3), or if the OFC result was positive but the infant had negative SPT responses and sIgE levels (peanut, n = 3; egg, n = 26; and sesame, n = 3). Data from inconclusive challenges were excluded from the analysis.

SPTs were available for 435, 650, 167, and 103 conclusive peanut, raw egg, baked egg, and sesame OFCs, respectively; serum was available for 370, 557, 143, and 85 conclusive peanut,

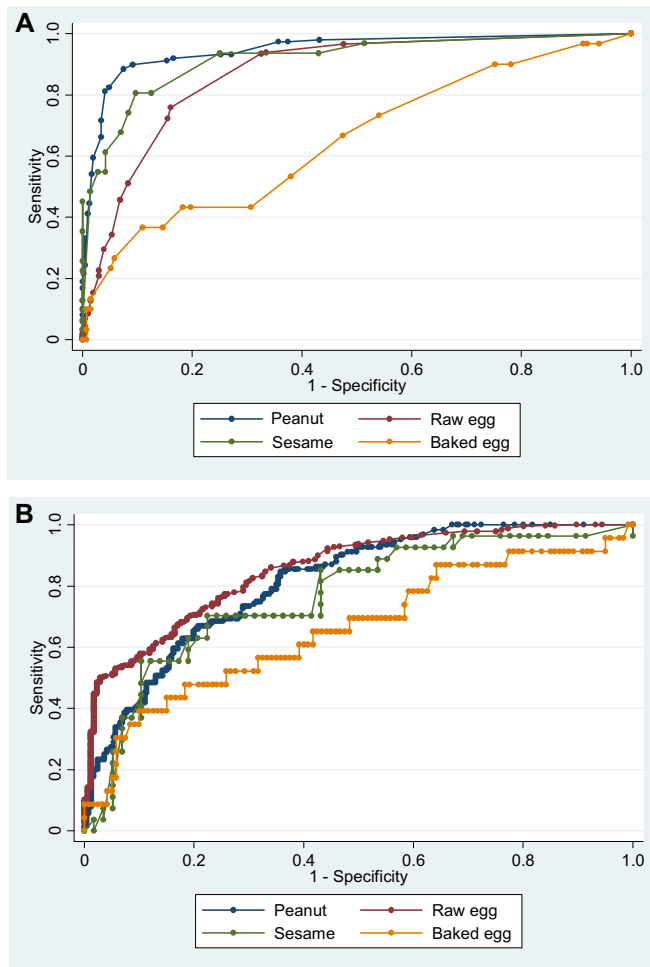
raw egg, baked egg and sesame OFCs, respectively. The demographic characteristics of the sample are presented in Table I. Thirty of 185 infants who participated in OFCs with egg in baked goods had positive results for allergy.

## SPTs

SPT thresholds with 95% PPVs for food allergy, along with sensitivity, specificity, NPV, positive and negative LR, and AUC for each threshold, are presented in Table II. SPT thresholds with 95% PPVs for food allergy are 8 mm or greater for peanut (95% CI, 7-9 mm), 4 mm or greater for egg (95% CI, 3-5 mm), and 8 mm or greater for sesame (95% CI, 5-9 mm). A graphic representation of the relationship between sensitivity and specificity, as calculated by using ROC curves, is presented in Fig 1, A. AUCs were high for peanut, egg, and sesame SPTs (0.93, 0.87, and 0.92, respectively). No SPT threshold had a 95% PPV for baked egg allergy; however, an 82% PPV was calculated at 11 mm. The AUC was low (0.65), and therefore the egg SPT is a poor predictor of allergy to egg in baked goods. Specificity for given thresholds was very high for each allergen. There was no significant difference between SPT 95% PPVs after stratification on known risk factors for food allergy (data not shown).

## Serum-specific IgE testing

Serum-specific IgE thresholds with 95% PPVs for food allergy, along with sensitivity, specificity, NPV, positive and negative LR, and AUC, are presented in Table III. ROC curves are presented in Fig 1, B. Peanut sIgE levels of 34 kU<sub>A</sub>/L or greater (95% CI, 14-48 kU<sub>A</sub>/L) and egg sIgE levels of 1.7



**FIG 1.** ROC curves for SPT wheal size (**A**) and sIgE level (**B**) to egg, baked egg, peanut, and sesame allergy.

kU<sub>A</sub>/L or greater (95% CI, 1-3 kU<sub>A</sub>/L) had 95% PPVs for challenge-proved food allergy. The AUC was high for egg and peanut sIgE levels but poor for baked egg and sesame sIgE levels. No sIgE threshold had a 95% PPV to baked egg allergy or sesame allergy. There was no significant difference between 95% PPVs after stratification on known risk factors for food allergy (data not shown), with the exception of peanut sIgE in infants who had previously reacted to peanut. sIgE thresholds with 95% PPVs to peanut allergy were 1.0 kU<sub>A</sub>/L or greater (95% CI, 0-4 kU<sub>A</sub>/L) and 39 kU<sub>A</sub>/L or greater (95% CI, 18-49 kU<sub>A</sub>/L) for infants with and without a previous reaction history, respectively.

### Probability curves

For infants whose test results fell into the indeterminate area (ie, <95% PPV decision point), the probability of food allergy for cumulative SPT responses and sIgE levels that exceed the given threshold was calculated in Fig 2. These graphs represent the probability of food allergy for infants with SPT responses or sIgE levels equal to or greater than the stated threshold. These probabilities are generated from infants with detectable SPT responses or sIgE levels.

### DISCUSSION

This is the largest cohort of infantile food challenges ever undertaken and provides unique data unlikely to be replicated because we had ethical approval to undertake OFCs in this cohort of infants with detectable SPT responses, irrespective of the magnitude of the wheal size. This enables us to provide novel data that inform SPT and sIgE 95% PPV thresholds across the full spectrum of SPT responses and sIgE levels in infants less than 2 years of age. This is also the first study to assess systematically whether the presence of risk factors for food allergy alter the predictive value of these tests. We found that an SPT wheal size of 8 mm or greater for peanut, 4 mm or greater for egg, and 8 mm or greater sesame and sIgE levels of 34 kU<sub>A</sub>/L or greater for peanut and 1.7 kU<sub>A</sub>/L or greater for egg have 95% PPVs to food allergy. These thresholds did not alter on stratification for known risk factors for food allergy, apart from previous history of reaction to peanut. The SPT response was a poor predictor of baked egg allergy, and the sIgE level was a poor predictor of baked egg and sesame allergy.

The strengths of the HealthNuts study are the large sample size, high participation fraction, and good internal and external validity.<sup>7</sup> The outcome was the gold standard OFC with predetermined objective criteria, which was offered to all infants with detectable SPT responses. By challenging all infants with detectable SPT responses, the classification of food allergy is robust compared with relying on clinical history or tests of sensitization alone.

In the nonsensitized infants 71 (1.72%) of 4064, 15 (0.34%) of 4393, and 3 (0.06%) of 4787 parents reported an adverse reaction to egg, peanut, and sesame, respectively, at some time in the infant's first year of life. Because these infants were nonsensitized at 12 months of age and because all of the random sample of 200 negative control (nonsensitized) infants had challenge-confirmed tolerance, we believe that there is strong evidence that these nonsensitized infants who reported a reaction to a food do not have current IgE-mediated food allergy.

A potential limitation of our study is that open OFCs were used rather than double-blind, placebo-controlled food challenges; however, only objective symptoms were used to define a positive OFC result, and the validity and sufficiency of using open challenges in infants has been previously confirmed independently.<sup>8</sup>

Our threshold for peanut SPT response is larger than previously reported in infants of a similar age; however, the previous sample consisted of a smaller number of infants from a highly selected clinic population.<sup>4,9</sup> Our results for egg SPTs are comparable with previously reported thresholds in infants of a similar age<sup>4,10,11</sup> and smaller than thresholds reported from mixed age groups, which ranged from 7 to 13 mm.<sup>4,12,13</sup>

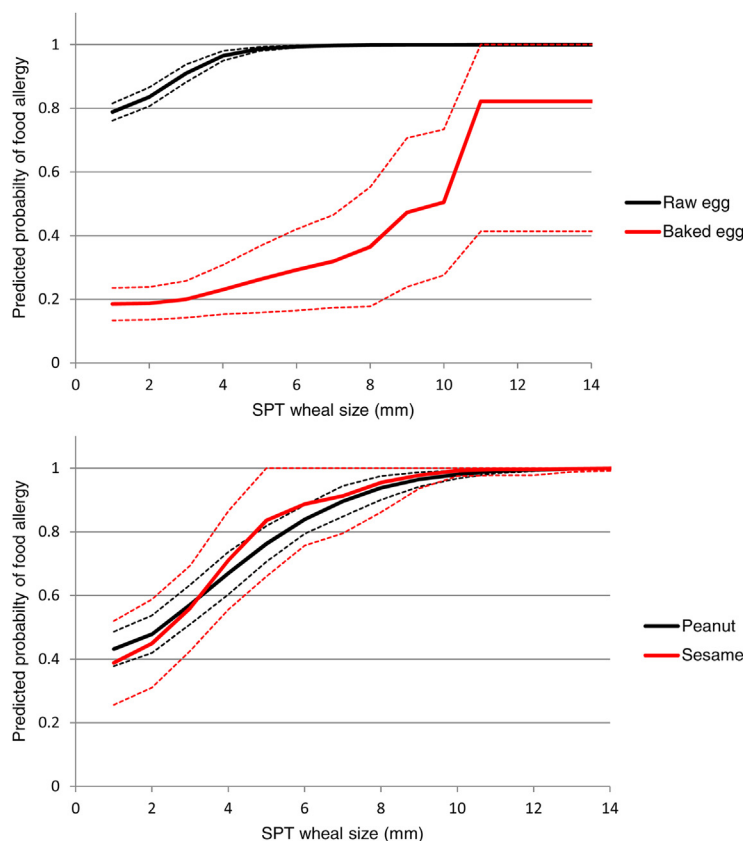
Several studies have established sIgE thresholds with 95% PPVs to egg allergy in infants with similar ages to this study, ranging from 0.35 kU<sub>A</sub>/L to 23 kU<sub>A</sub>/L.<sup>3,10,14</sup> Similar discrepancies are seen with peanut allergy, although an sIgE level of 15 kU<sub>A</sub>/L or greater is commonly quoted.<sup>15,16</sup> These differences can be attributed to differences in study populations and test methods. Stratification revealed that infants with a history of reacting to peanut had a lower sIgE threshold ( $\geq 1.0$  kU<sub>A</sub>/L) compared with those without a history of reaction ( $\geq 39$  kU<sub>A</sub>/L). The former threshold can be used in infants presenting with a clinical history suggestive of peanut allergy. In contrast, the threshold identified in infants without a history of reaction will be suitable



**TABLE III.** Diagnostic capacity of sIgE measurements to challenge-confirmed IgE-mediated food allergy

Allergen	No.	95% PPV (kU <sub>A</sub> /L [95% CI])	NPV (% [95% CI])	Sensitivity (% [95% CI])	Specificity (% [95% CI])	Positive LR (95% CI)	Negative LR (95% CI)	AUC (95% CI)
Peanut	370	34 (13.5-48.0)	69 (64-74)	14 (8-21)	99 (96-100)	11.2 (3.4-37.6)	0.87 (0.81-0.94)	0.81 (0.77-0.86)
Egg	557	1.7 (0.9-3.1)	47 (41-52)	48 (43-53)	98 (94-99)	21.2 (8.0-56.3)	0.53 (0.48-0.59)	0.85 (0.82-0.89)
Baked egg	143	50 (88% PPV)*	85 (78-90)	9 (1-28)	100 (97-100)	-	0.91 (0.80-1.04)	0.66 (0.53-0.80)
Sesame	85	50 (86% PPV)*	69 (58-78)	4 (0-19)	98 (91-100)	2.2 (0.1-33.1)	0.98 (0.90-1.06)	0.76 (0.65-0.88)

\*Ninety-five percent PPVs could not be calculated.

**FIG 2.** The probability of food allergy for infants with SPT responses and sIgE levels equal to or greater than the stated threshold.

for use as a screening tool in infants who are yet to consume peanut. This threshold ( $\geq 39$  kU<sub>A</sub>/L) is considerably higher than previously reported thresholds. Eight of 37 infants with sIgE levels of 20 kU<sub>A</sub>/L or greater were tolerant to peanut on OFCs. These 8 infants only had moderate SPT wheal sizes (3-5 mm).

Our results agree with previous findings that SPT response is a poor predictor of baked egg allergy and that sIgE level is a poor predictor of baked egg and sesame allergy.<sup>17-21</sup> However, we were able to add to existing knowledge by developing probability curves for increasing SPT responses and sIgE levels, which will assist clinicians in determining their patients' risk of food allergy. For SPTs, we used an egg white extract. Different results might be obtained for baked egg allergy if a different egg extract or fresh food were used.

It must be noted that if the sensitivity and specificity are assumed to be fixed, then PPVs and NPVs are dependent on the underlying prevalence of food allergy. Despite this, we believe that they provide additional diagnostic value beyond sensitivity or specificity alone. Ninety-five percent PPVs provide clinicians

with an SPT or sIgE threshold above which their patients are highly likely to have food allergy and therefore allows the patient to avoid an unnecessary OFC. The LR, which compares the probability of a positive SPT or sIgE test result in patients with and without food allergy, is a function of sensitivity and specificity. LRs overcome the limitations of PPVs because they are not dependent on the prevalence of food allergy and can be transferred to a clinician's own setting. This method relies on the clinician estimating his or her patient's pretest probability of food allergy, and using the Fagan nomogram in conjunction with the LR will produce an estimate of the patient's posttest probability of food allergy.<sup>22,23</sup>

The PPVs were calculated by using data from a group of sensitized infants among whom the food allergy prevalence was similar to those generated from other studies (in which participants were recruited from allergy clinics), despite the fact that they were selected from a population-based sample irrespective of reaction history or other risk factors for food allergy. Because the calculation of the empiric PPVs (which we then smoothed using a

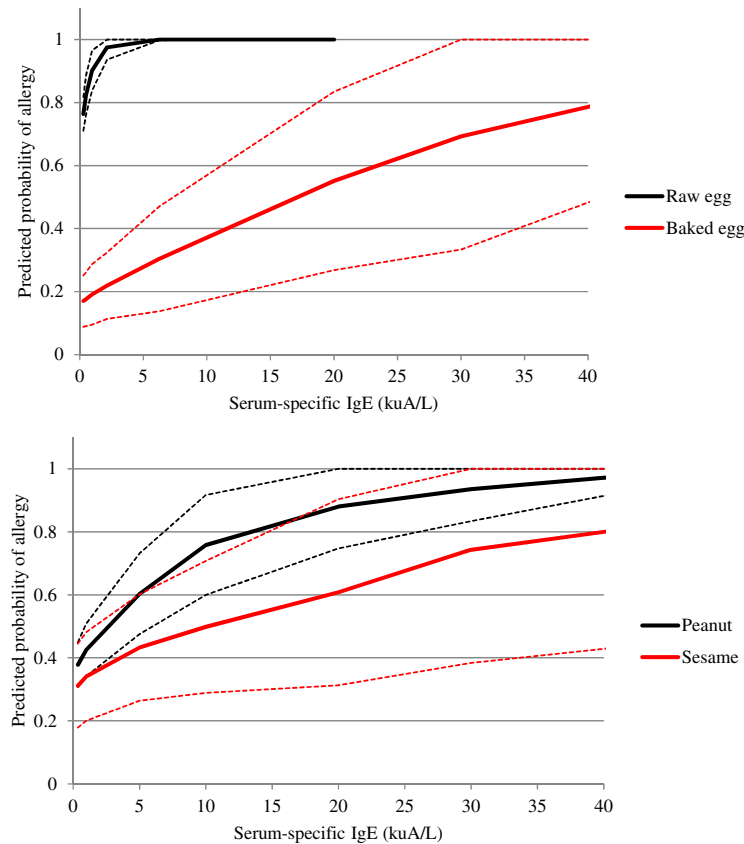


FIG 2. (Continued)

logistic regression model) is based only on the participants with positive test results (sensitized) for OFC-confirmed allergy, the inclusion of data from the additional 4000 nonsensitized (negative test results) infants would not change these results. It should be noted that the NPVs presented are conservative because the sample included only those infants with detectable SPT responses at community recruitment and should be interpreted with caution in other clinical settings.

Using ROC analysis, we found that the SPT response was more precise than the sIgE level at predicting sesame and peanut allergy in infants with no reaction history; performance was similar for egg allergy. Component-resolved diagnostics, particularly measurement of sIgE levels to Ara h 2, has shown promising results and is more precise at predicting peanut allergy than sIgE levels to whole peanut alone.<sup>24,25</sup> The advent of other forms of component-resolved diagnostics, particularly for egg and other common food allergies, might provide significant improvement in the reliability of sIgE testing in the future.

In conclusion, these findings are likely to inform clinical practice in the care of young children with food allergy. Information about how 95% PPVs perform in predicting the development of tolerance will become available because this cohort is now being followed to age 6 years.

The HealthNuts Investigators also include Melissa Wake, Melanie Matheson, Dean Tey, Leone Thiele, Deborah Anderson, Lucy Miles, Tina Tan, Thanh Dang, Margaret Sutherland, Helen Czech, Kelley Mancner, Mark Nethercote, Marjolein Slaa, Stephanie Almer, Jeeva Sanjeevan, and Giovanni Zurzolo. We thank the children and parents who participated in the HealthNuts Study, as well as the staff of Melbourne's Local Government Areas for access

to community immunization clinics. We thank ALK-Abelló S.A., Madrid, Spain, for supplying the SPT reagents and the HealthNuts safety committee: Associate Professor Noel Cranswick (Australian Paediatric Pharmacology Research Unit/Murdoch Childrens Research Institute), Dr Jo Smart (Department of Allergy and Immunology, Royal Children's Hospital, Melbourne, Australia), and Associate Professor Jo Douglass (Director of Allergy and Immunology Royal Melbourne Hospital, Melbourne, Australia).

#### Key messages

- In a large cohort of infants who received OFCs irrespective of wheal size or previous history of ingestion, 95% PPVs for peanut and sesame SPT were 8 mm or greater, and those for egg SPT were 4 mm or greater; 95% PPVs for peanut sIgE were 34 kU<sub>A</sub>/L or greater, and those for egg sIgE were 1.7 kU<sub>A</sub>/L or greater.
- SPT 95% PPVs were unaffected by other associated risk factors for food allergy, including infantile eczema, family history, and vitamin D status.
- These PPVs are unique because they were generated irrespective of SPT responses, sIgE levels, or previous history of ingestion and will be invaluable for use in young children in whom food allergy is suspected.

#### REFERENCES

1. Sicherer SH, Sampson HA. Food allergy. *J Allergy Clin Immunol* 2010; 125(suppl 2):S116-25.
2. Jarvinen KM, Sicherer SH. Diagnostic oral food challenges: procedures and biomarkers. *J Immunol Methods* 2012;383:30-8.

3. Komata T, Soderstrom L, Borres MP, Tachimoto H, Ebisawa M. The predictive relationship of food-specific serum IgE concentrations to challenge outcomes for egg and milk varies by patient age. *J Allergy Clin Immunol* 2007;119:1272-4.
4. Sporik R, Hill DJ, Hosking CS. Specificity of allergen skin testing in predicting positive open food challenges to milk, egg and peanut in children. *Clin Exp Allergy* 2000;30:1540-6.
5. Liew WK, Williamson E, Tang ML. Anaphylaxis fatalities and admissions in Australia. *J Allergy Clin Immunol* 2009;123:434-42.
6. Keet CA, Wood RA, Matsui EC. Limitations of reliance on specific IgE for epidemiologic surveillance of food allergy. *J Allergy Clin Immunol* 2012;130:1207-9.e10.
7. Osborne NJ, Koplin JJ, Martin PE, Gurrin LC, Thiele L, Tang ML, et al. The HealthNuts population-based study of paediatric food allergy: validity, safety and acceptability. *Clin Exp Allergy* 2010;40:1516-22.
8. Venter C, Pereira B, Voigt K, Grundy J, Clayton CB, Gant C, et al. Comparison of open and double-blind placebo-controlled food challenges in diagnosis of food hypersensitivity amongst children. *J Hum Nutr Diet* 2007;20:565-79.
9. Hill DJ, Heine RG, Hosking CS. The diagnostic value of skin prick testing in children with food allergy. *Pediatr Allergy Immunol* 2004;15:435-41.
10. Boyano Martinez T, Garcia-Ara C, Diaz-Pena JM, Munoz FM, Garcia Sanchez G, Esteban MM. Validity of specific IgE antibodies in children with egg allergy. *Clin Exp Allergy* 2001;31:1464-9.
11. Monti G, Muratore MC, Peltran A, Bonfante G, Silvestro L, Oggero R, et al. High incidence of adverse reactions to egg challenge on first known exposure in young atopic dermatitis children: predictive value of skin prick test and radioallergen sorbent test to egg proteins. *Clin Exp Allergy* 2002;32:1515-9.
12. Dieguez MC, Cerecedo I, Muriel A, Zamora J, Abaira V, Camacho E, et al. Utility of diagnostic tests in the follow-up of egg-allergic children. *Clin Exp Allergy* 2009;39:1575-84.
13. Verstege A, Mehl A, Rolinck-Werninghaus C, Staden U, Nocon M, Beyer K, et al. The predictive value of the skin prick test wheal size for the outcome of oral food challenges. *Clin Exp Allergy* 2005;35:1220-6.
14. Celik-Bilgili S, Mehl A, Verstege A, Staden U, Nocon M, Beyer K, et al. The predictive value of specific immunoglobulin E levels in serum for the outcome of oral food challenges. *Clin Exp Allergy* 2005;35:268-73.
15. Roberts G, Lack G. Diagnosing peanut allergy with skin prick and specific IgE testing. *J Allergy Clin Immunol* 2005;115:1291-6.
16. Sampson HA, Ho DG. Relationship between food-specific IgE concentrations and the risk of positive food challenges in children and adolescents. *J Allergy Clin Immunol* 1997;100:444-51.
17. Maloney JM, Rudengren M, Ahlstedt S, Bock SA, Sampson HA. The use of serum-specific IgE measurements for the diagnosis of peanut, tree nut, and seed allergy. *J Allergy Clin Immunol* 2008;122:145-51.
18. Permaul P, Stutius LM, Sheehan WJ, Rangsihienchai P, Walter JE, Twarog FJ, et al. Sesame allergy: role of specific IgE and skin-prick testing in predicting food challenge results. *Allergy Asthma Proc* 2009;30:643-8.
19. Zavalkoff S, Kagan R, Joseph L, St-Pierre Y, Clarke A. The value of sesame-specific IgE levels in predicting sesame allergy. *J Allergy Clin Immunol* 2008;121:1508-10.
20. Cortot CF, Sheehan WJ, Permaul P, Baxi SN, Gaffin JM, Dioun AF, et al. Role of specific IgE and skin-prick testing in predicting food challenge results to baked egg. *Allergy Asthma Proc* 2012;33:275-81.
21. Ho MH, Heine RG, Wong W, Hill DJ. Diagnostic accuracy of skin prick testing in children with tree nut allergy. *J Allergy Clin Immunol* 2006;117:1506-8.
22. Roberts G, Lack G. Food allergy—getting more out of your skin prick tests. *Clin Exp Allergy* 2000;30:1495-8.
23. Fagan TJ. Letter: nomogram for Bayes theorem. *N Engl J Med* 1975;293:257.
24. Dang TD, Tang M, Choo S, Licciardi PV, Koplin JJ, Martin PE, et al. Increasing the accuracy of peanut allergy diagnosis by using Ara h 2. *J Allergy Clin Immunol* 2012;129:1056-63.
25. Nicolaou N, Poorafshar M, Murray C, Simpson A, Winell H, Kerry G, et al. Allergy or tolerance in children sensitized to peanut: prevalence and differentiation using component-resolved diagnostics. *J Allergy Clin Immunol* 2010;125:191-7.e1-13.